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Review

Role of Metabolic Nutrition in Newborn Screening and Inherited Metabolic Disorders

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Abstract

The expansion of newborn screening (NBS) encompasses a wide range of inherited metabolic disorders, including disorders of carbohydrate, lipid, and protein metabolism. Effective treatment of these disorders requires comprehensive nutrition and medical management. This review highlights the intricacies of medical nutrition therapy for several common metabolic disorders and underscores the crucial role of metabolic dietitians in managing these patients.

Keywords

Metabolic dietitian; newborn screening; inherited metabolic disorders; medical nutrition therapy

1. Introduction

The primary objective of the newborn screening (NBS) program is to achieve affordable and timely detection of treatable disorders, emphasizing the importance of prompt intervention to enhance long-term outcomes [1]. The NBS program operates at the state level in the United States, resulting in some variation in the disorders screened. However, the Advisory Committee on Heritable Disorders in Newborns and Children recommends a set of conditions that all states include in their screening protocols [1]. Since the initial development of the first NBS test for phenylketonuria (PKU), significant progress has been achieved in newborn screening, and patient outcomes have improved for all of the disorders in the core NBS panel [1, 2]. Recent technological advancements have facilitated the expansion of NBS to include disorders of carbohydrate, lipid, and protein metabolism, among others. Most of these newly screened metabolic disorders are treatable with comprehensive nutrition and medical management.

Medical management of patients with metabolic disorders requires a team approach, including geneticists, metabolic dietitians, genetic counselors, nurses, and social workers. Metabolic dietitians are registered dietitians with specialized training in providing medical nutrition therapy to patients with inherited metabolic disorders using the latest evidence-based methods. They utilize a comprehensive approach, incorporating physical, clinical, and laboratory data to administer complex medical nutrition therapy that provides appropriate nutrition to support growth and development while limiting the offending substrate. While not exhaustive, this review will highlight the complex medical nutrition therapy of several common metabolic disorders and the central role metabolic dietitians play in managing these patients.

2. Nutrition Management of Specific Metabolic Disorders

2.1 Fatty Acid Oxidation Disorders (FAODs)

Fatty acid oxidation disorders (FAODs) are autosomal recessive inherited inborn errors of lipid metabolism due to deficiencies of either mitochondrial β-oxidation enzymes or carnitine transport enzymes. Most patients with FAODs are detected through NBS by measuring elevated acylcarnitines specific to each FAOD (Table 1). Molecular testing is necessary for confirmation and can help determine genotype-phenotype correlations [3]. Every year, approximately 100 infants are diagnosed with long-chain fatty acid oxidation disorders (LC-FAODs) in the United States, while the current population of individuals living with LC-FAOD is estimated to range between 2,000 and 3,5000 [4]. Some FAODs, such as medium-chain acyl-CoA dehydrogenase deficiency (MCADD), are more common than the LC-FAODs individually (Table 1); however, the worldwide incidence of LC-FAODs is about 1 in 9,300 individuals (Table 1) [4].

Table 1 Genetics and Presentation of FAODs [3-7].

FAOD	Gene	Incidence	Acylcarnitine Elevations	*Additional Complications
Medium-chain acyl-CoA dehydrogenase deficiency	*ACADM*	1:20,000	C8, C10, C10:1	--

(MCADD)				
Very long-chain acyl-CoA dehydrogenase deficiency (VLCADD)	*ACADVL*	1:40,000 – 120:000	C12:1, C14:2, C14:1, C14, C16:1, C16	--
Long-chain 3-hydroxy acyl-CoA dehydrogenase (LCHADD)	*HADHA*	1:250,000	C16:1-OH, C16-OH, C18:1-OH, C18-OH	Liver dysfunction (Reye-like syndrome), cholestasis, skeletal myopathy, pigmentary retinopathy, peripheral neuropathy
Trifunctional protein deficiency (TFPD)	*HADHA, HADHB*	<1:100,000 (estimated)	C16:1-OH, C16-OH, C18:1-OH, C18-OH	Peripheral neuropathy, retinopathy
Carnitine palmitoyl transferase type 1 deficiency (CPT1AD)	*CPT1A*	Undetermined Fewer than 50 affected individuals have been identified	C0 (low), C0/(C16:0 + C18) ratio	Renal tubular acidosis
Carnitine palmitoyl transferase type 2 deficiency (CPT2D)	*CPT2*	Undetermined	C16, C16:1, C18, C18:1	Renal cysts, facial dysmorphism
Carnitine-acylcarnitine translocase deficiency (CACTD)	*SLC25A20*	Undetermined	C16, C16:1, C18, C18:1	High mortality despite treatment

*Symptoms in addition to cardiomyopathy, heart failure, hypoketotic hypoglycemia, rhabdomyolysis, muscle weakness, and liver dysfunction

When fatty acids are needed as an energy source during exercise, prolonged fasting, or increased energy demands due to illness, surgery, or injury, fatty acids are oxidized in the mitochondria to supply energy to the cell [3]. Mitochondrial β-oxidation generates the reducing agents flavin adenine dinucleotide ($FADH_2$) and nicotinamide adenine dinucleotide (NADH), which donate electrons to the respiratory chain for oxidative phosphorylation and ATP generation, supplying a significant source of energy [3]. With deficient β-oxidation, patients with FAODs experience decreased energy production and increased production of abnormal fatty acid metabolites, yielding cardiomyopathy, heart failure, hypoketotic hypoglycemia, rhabdomyolysis, muscle weakness, liver dysfunction, and fatality depending on severity [3].

Common elements of nutrition management of all FAODs include fasting avoidance, aggressive treatment during illness, and carnitine supplementation only if deficient [3]. Fasting avoidance consists of a maximum of 3-4 hours between feedings for infants up to 4 months, with an increase of 1 hour of fasting for every additional month of age up to 10-12 hours after one year during times of wellness [3, 8]. Patients with mild/moderate severity can often tolerate longer fasting times. FAOD patients require carbohydrate-rich fluids/foods every 3-4 hours during mild illnesses. During severe illnesses, FAOD patients may require intravenous (IV) fluids with 10 percent dextrose at a 1.5 times maintenance fluid rate (equivalent to a glucose infusion rate of 8 mg/kg/min) with appropriate electrolytes as outlined in their emergency treatment letter [3, 8]. Infusion of IV lipids

is contraindicated; however, a source of essential fatty acids should be provided if intake remains inadequate after seven days [8].

In addition to common nutrition therapy elements, treatment for Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) also includes avoidance of medium-chain triglyceride (MCT) oil, which can be challenging as specialty infant and pediatric formulas often contain high sources of MCT (outlined in detail in Merritt, et al., 2018) [3]. Overall, patients with MCADD are educated to consume a regular, healthy diet [3].

In contrast to MCADD, patients with long-chain fatty acid oxidation disorders (LC-FAODs) require a fat-restricted diet as a means for limiting substrate for mitochondrial β-oxidation and MCT supplementation to bypass the deficient enzyme and still produce acetyl CoA [3]. The degree of dietary fat restriction depends on the patient's disease severity as determined by gene variants or clinical symptoms [8]. It gradually increases as the patient ages, with severe patients still limited to 10% of total energy from long-chain fat and 20-30% from MCT (Table 2) [8]. Infants require low-fat, MCT-supplemented formulas (medical food), and older children/adults receive their MCT from pharmaceutical grade MCT® oil or powdered MCT products (Table 3) [8]. Given the extent of fat restriction, patients may need to include oils rich in essential fatty acids as part of their daily fat allowance to prevent deficiency [3, 8]. Supplementation of essential fatty acids and fat-soluble vitamins may be necessary.

Table 2 *Nutrient needs for VLCADD Based on Age and Disease severity [8, 9].

Age	Disease Severity	Total fat (% of total energy)	LCFA (% of total energy)	MCT (% of total energy)	Energy [10]	Protein (g/kg/day) RDA for age
0-6 months	Severe	40-55	10-15	30-45	EER	>1.5
	Moderate		15-30	10-30		
	Mild		30-55	0-20		
7-12 months	Severe	35-45	10-15	25-30	EER	>1.2
	Moderate		15-30	10-25		
	Mild		30-40	0-10		
1-3 years	Severe	30-40	10-15	10-30	EER	>1.1
	Moderate		20-30	10-20		
	Mild		20-40	0-10		
4-18 years	Severe	25-35	10	15-25	EER + PAL	0.85-0.95
	Moderate		15-25	10-20		
	Mild		25-35	0-10		
>19 years	Severe	20-35	10	10-25	EER + PAL	0.8
	Moderate		15-20	10-20		
	Mild		25-35	0-10		
Pregnancy	Severe	20-35	10	10-25	Trimester 1 = EER for age Trimester 2 = EER pre-pregnancy + 340 kcal	1.1
	Moderate		15-20	10-20		
	Mild		25-35	0-10		

					Trimester 3 = EER pre-pregnancy + 452 kcal	
Lactation	Severe Moderate Mild	20-35	10 15-20 25-35	10-25 10-20 0-10	EER	1.3

Estimated energy requirement (EER) recommended by the Institute of Medicine (IOM) [10]; physical activity level (PAL). *Recommendations published specifically for VLCADD; however, they are helpful for prescribing medical nutrition therapy for other LC-FAODs.

Table 3 Selected Medical Foods for FAODs [9].

Company	Infant Products	Pediatric Products		MCT-Free Products
	Complete	Complete	*Incomplete	*Incomplete
Mead Johnson	Enfaport™	Portagen®		
Nutricia	Monogen®		Liquigen®	**Milupa Basic F® (Fat-Free)
Nestle			MCT Oil®	VIVONEX® T.E.N (Very Low-Fat) Tolerex® (Very Low-Fat)
Vitaflo	LIPIstart™ (Birth to 10 years)		MCT Procal® Betaqiuk®	

Mead Johnson Nutrition, Evansville, IN; Nestle Healthcare Nutrition, Bridgewater, NJ; Nutricia North America, Rockville, MD; Vitaflo USA, Alexandria, VA.*Incomplete formulas are low in or devoid of fat, carbohydrate, vitamins and/or minerals. **Not available in the United States

Triheptanoin (DOJOLVI® Ultragenyx Pharmaceutical Inc.) is a newly FDA-approved therapeutic for treating LC-FAODs (Table 4) [11]. Triheptanoin comprises three odd-chain 7-carbon fatty acids on a glycerol backbone that enter the mitochondria without a carnitine carrier (similar to MCT), bypassing the enzymes that metabolize long-chain fatty acids and are oxidized to generate both acetyl-CoA and propionyl-CoA which enter the tricarboxylic acid (TCA) cycle [11]. Due to the formation of both acetyl-CoA and propionyl-CoA instead of solely acetyl-CoA, Triheptanoin is more effective than MCT oil at replenishing TCA cycle intermediates. One challenge of using Triheptanoin is that patients must discontinue all MCT-containing medical foods due to potential competitive inhibition [12]. The dietitian must construct a complete nutrition prescription by combining various MCT-free medical foods to meet 100% nutrient needs, including fat, protein, carbohydrates, vitamins, and minerals. In addition to standard low-fat, MCT-supplemented medical foods for patients with LC-FAODs, Table 3 includes MCT-free medical foods that are low or devoid of fat and can be used as a base for a patient on Triheptanoin. In a Triheptanoin extension study, there was a 70% median annualized reduction in the incidence and frequency of hospital days due to major clinical events (rhabdomyolysis, hypoglycemia, and cardiomyopathy) in patients who previously were on MCT oil [13]. Despite significant advances, rhabdomyolysis, and cardiomyopathy continue to cause morbidity and mortality among patients with severe forms of LCFAOD's [3, 13].

Table 4 Common Medications/Supplements used to treat LC-FAODs.

Medication/Supplement	Mechanism of Action	Considerations
DOJOLVI®[a] (triheptanoin)	Bypass enzymes that metabolize long-chain fatty acids to replenish TCA cycle intermediates [11].	patients must discontinue all MCT-containing medical foods due to potential competitive inhibition [12].

[a]Ultragenyx Pharmaceutical Inc, Novato, CA

Routine monitoring of echocardiogram, acylcarnitine profile, creatine kinase, essential fatty acids, complete blood count (CBC), comprehensive metabolic panel (CMP), 25-OH vitamin D, fat-soluble vitamins, troponin, and B-natriuretic protein is crucial [8]. Typically, the laboratory tests are monitored weekly to monthly for the first three months and then spaced out to every six months or yearly, depending on clinical symptoms [8].

2.2 Galactosemia

Galactosemia is an inherited disorder of galactose metabolism. There are four types of galactosemia, each affecting a different step in galactose metabolism: Classic or type I galactosemia due to a deficiency in the enzyme galactose-1-phosphate uridylyltransferase (GALT), type II galactosemia due to a deficiency in galactokinase (GALK), type III galactosemia due to a deficiency in UDP-galactose 4 epimerase (GALE), and type IV galactosemia due to a deficiency in galactose mutarotase (GALM) [14, 15]. Classic galactosemia is the most severe type and is the focus of this review.

As a result of deficient GALT activity, galactose-1-phosphate (gal-1-P) and galactitol build up, leading to various health issues affecting multiple organs [14]. These complications include liver disease, sepsis caused by E. coli infection, cataracts, speech impairment, renal tubular dysfunction, impaired growth, and ovarian dysfunction in females [14]. Diagnosis of classic galactosemia is confirmed with the measurement of gal-1-P or GALT enzyme activity through NBS in addition to GALT gene analysis [14]. Classic galactosemia is an autosomal recessive disorder with a prevalence of 1:16,000 to 1:50,000 live births in Western countries [15].

In cases where classic galactosemia is suspected in an infant, clinicians should promptly discontinue breastmilk or milk-based infant formulas and initiate a diet that restricts galactose intake (such as soy-based or elemental formula) without waiting for confirmation of the diagnosis [14, 16]. A lifelong galactose-restricted diet is recommended for patients with classic galactosemia and should primarily focus on eliminating lactose (glucose + galactose) and galactose from dairy products while allowing for minimal dietary galactose from non-milk sources (Table 5) [14]. Galactose within the plant cell wall (called “bound” galactose) is found in many fruits, vegetables, legumes, nuts, and seeds [16]. Recent studies demonstrate that bound galactose does not add to the free galactose pool in the body, so the treatment of classic galactosemia allows any amount and type of fruits, vegetables, legumes, unfermented soy-based products (Table 5) [14]. Additionally, some mature cheeses and sodium or calcium caseinate are allowed since they are extensively aged or processed to significantly reduce the lactose and galactose content (Table 5) [14]. The goal is to restrict galactose to the lowest amount compatible with a nutritionally adequate diet to support age-appropriate growth and development [16]. As a galactose-restricted diet is naturally low in

calcium and vitamin D, it is essential to meet both calcium and vitamin D needs through soy-based formulas, elemental formulas, or individual supplementation [16].

Table 5 Current Diet Restrictions for Galactosemia [14, 16, 17].

***Allowed foods and ingredients**
Soy-based infant formulas containing soy protein isolate, amino acid-based elemental infant formulas
All fruits, vegetables and their juices, pickled fruit, and vegetables
All legumes (e.g., navy beans, kidney beans, garbanzo beans/chickpeas, soybeans)
Soy-based products that are not fermented (soy milk, tofu, textured soy protein, hydrolyzed vegetable protein, soy protein concentrate, meat analogs)
**Aged cheeses: Jarlsberg, Emmentaler, Swiss, Gruyere, Tilsiter, mature Parmesan, mature Cheddar cheese
Sodium and calcium caseinate
All cacao products except milk chocolate
Eggs
Additional ingredients: natural and artificial flavorings, all gums, including carrageenan
***Foods used in moderation**
Soy sauce, soy products that are fermented (e.g., miso, natto, tempeh, tofu)
Meat by-products
Offal (organ meats)
***Restricted foods and ingredients**
Breastmilk, all milk-based infant formulas
Processed meats using lactose
All milk-based foods and beverages, including low lactose milk, except for caseinates and aged cheeses, listed above
All milk-based ingredients, including buttermilk solids, casein, dry milk protein, dry milk solids, hydrolyzed whey protein, hydrolyzed casein protein, lactose, lactalbumin, whey
All cheese and cheese-based products except those listed above
Butter

* All manufactured foods need to be checked for the presence of milk by reading food ingredient labels. ** Galactose content and consequently allowed types of cheese may vary in different countries

Laboratory monitoring is essential in the management of classic galactosemia including measurement of Gal-1-P in red blood cells at diagnosis, 3 months and 9 months [14]. Additionally, it is crucial to measure 25-OH vitamin D levels at least annually [14, 16]. Despite the strict elimination of galactose from the diet, patient outcomes are variable [14, 16]. More details on Galactosemia are discussed in another article in this special issue by Hong & He.

2.3 Glutaric Acidemia Type 1 (GA-1)

GA-1 is an autosomal recessive neurometabolic disorder of lysine metabolism caused by pathogenic variants in the glutaryl-CoA dehydrogenase (GCDH) gene, resulting in a deficiency of mitochondrial GCDH with an estimated worldwide incidence of 1:90,000-1:120,000 newborns [18].

This deficiency leads to the accumulation of glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA), glutaconic acid, and glutarylcarnitine (C5DC) [18]. These metabolites can be detected in urine and plasma using gas chromatography/mass spectrometry (for organic acids) and tandem mass spectrometry (for acylcarnitines and NBS) [18].

Most untreated individuals experience the sudden onset of striatal damage before 3 to 6 years, triggered by infectious diseases, fever, or surgery [18]. This damage results in an irreversible and disabling movement disorder, primarily dystonic, with a limited life expectancy [18].

Early detection through newborn screening is crucial for starting metabolic treatment before symptoms appear. This treatment includes a low lysine diet (Table 6 and Table 7), supplementation with carnitine (Table 8), and intensified emergency treatment during illnesses or surgeries [18]. These interventions have significantly improved the neurological outcomes in patients with GA-1. However, metabolic treatment cannot reverse the motor dysfunction caused by striatal damage [18]. The goal of nutrition therapy for GA-1 is to restrict lysine intake using lysine-free medical foods (Table 6 and Table 7) while providing sufficient lysine through intact protein sources such as breast milk, infant formulas, or food to meet lysine goals (Table 7). Arginine competes with lysine for uptake across the blood-brain barrier and is, therefore, supplemented in GA-1 medical foods [18] There is no evidence for maintenance or emergent supplementation of arginine orally or IV [18]. Although riboflavin supplementation has been reported to decrease GA and 3-OH-GA concentrations, there is no evidence that riboflavin improves patient outcomes [18]. The dietary restrictions can be eased after the vulnerable period for striatal damage, typically around 6 years of age [18]. Nevertheless, the long-term effects of relaxing the dietary restrictions on overall outcomes remain uncertain.

Table 6 GA-1 Nutrient Needs by Age [18].

Age	Lysine (mg/kg/day)	Total Protein (g/kg/day)
0-6 months	65-100	2.75-3.5
6-12 months	55-90	2.5-3.25
1-4 years	50-80	1.8-2.6
4-7 years	40-70	1.6-2.0
>6 years	Consider liberalization of protein intake to age-appropriate DRIs [18]	

Table 7 Selected Medical Foods for GA-1 [19].

Company	Infant Products	Pediatric Products		Protein Free Modulars
	Complete	Complete	*Incomplete	
Abbott	Glutarex-1®	Gutarex-2®		Pro-Phree®
Mead Johnson	GA®	GA®		PFD Toddler (Infant)® PFD 2 (Pediatric)®
Nutricia	GA-1 Anamix® Early Years	GlutarAde Jr™ GA-1 Drink Mix	GlutarAde™ Essential	Duocal® Polycal®

Vitaflo	GlutarAde™ Essential GA-1 Drink Mix	Amino Acid Blend®	
		GA gel™	S.O.S™
		GA express 15®	10, 15, 20, 25

Abbott Nutrition, Lake Forest, IL; Cambrooke, Ayer, MA; Mead Johnson Nutrition, Evansville, IN; Nutricia North America, Rockville, MD; Vitaflo USA, Alexandria, VA. *Incomplete formulas are low in or devoid of fat, carbohydrate, vitamins and/or minerals.

Table 8 Common Medications/Supplements used to treat GA-1.

Medication/Supplement	Mechanism of Action	Considerations
L-carnitine	Binds with toxic Acyl-CoA metabolites and excretes them through urine	Excessive L-carnitine is associated with a fishy odor, gastrointestinal symptoms, and may increase the risk of atherosclerosis [20]

Routine laboratory monitoring of plasma amino acids and carnitine is crucial in GA-1 [18]. Typically, these laboratory tests are monitored every three months until age one and then spaced out to every six months or yearly, depending on clinical symptoms. Research does not support using GA or 3-OH-GA as a biomarker for management as they do not correlate to patient outcomes [18].

2.4 Maple Syrup Urine Disease (MSUD)

MSUD is an autosomal recessive inborn error of branched-chain amino acid (BCAA) metabolism. MSUD is caused by a deficiency of the branched-chain keto acid dehydrogenase enzyme complex, leading to the accumulation of leucine, valine, and isoleucine as well as their ketoacids (alpha-ketoisocaproic acid, keto-isovalerate and keto-beta-methylvalerate) [21, 22]. Of the accumulated BCAAs, leucine and its ketoacid, alpha-ketoisocaproic acid, are the toxic compounds that cause the clinical manifestations of MSUD [22]. Patients with MSUD are flagged through newborn screening with the detection of elevated leucine. MSUD was first discovered in 1954 by Menkes, Hurst, and Craig, who noticed a maple syrup odor in the urine of infants who died from a neurological disease [23]. In the general population, MSUD is quite rare, with a prevalence of 1 in 200,000 live births [22]; however, it is more common in the Mennonite population, with a prevalence of 1 in 350 live births [22].

Patients with MSUD present with classic, intermediate, or intermittent forms. The classic form of MSUD presents with neonatal onset, poor feeding, lethargy, altered tone, ketoacidosis, seizures, and developmental delays [22]. The intermediate form of MSUD develops slower with progressive failure to thrive, ketoacidosis, developmental delays, and classic symptoms during catabolic illness [22]. The intermittent form of MSUD presents with typical development, episodic ataxia, and ketoacidosis and is typically precipitated by illness or increased protein intake [22].

Treatment of MSUD consists of a low leucine diet to maintain near-normal plasma leucine levels (100-200 µmol/L for patients <5 years old and 100-300 µmol/L for patients >5 years old) [22]. It is essential first to determine the goals for leucine (mg), total protein (g), and energy (kcal) as they will be used to calculate the amount of leucine (breast milk, infant formula, food), BCAA-free medical food and calories needed to meet the patient's individual needs (Table 9) [22, 24]. The use of BCAA-

free medical foods is essential to provide patients with total protein above the daily recommended intake (DRI) (Table 9 and Table 10) [22]. Some variant forms of MSUD also respond to thiamine supplementation at 50-200 mg/d [24]. While it is essential to reduce leucine intake to maintain leucine concentrations in the normal range, valine and isoleucine can quickly deplete and lead to protein deficiency. Therefore, valine and isoleucine supplementation are crucial to prevent deficiency and help lower plasma leucine levels [22, 24].

Table 9 MSUD Nutrient Needs by Age [22].

Age	Leucine mg/kg/day	Isoleucine mg/kg/day	Valine mg/kg/day	Total Protein g/kg/day	Energy kcal/kg/day
0-6 mo	40-100	30-90	40-95	2.5-3.5	95-145
7-12 mo	40-75	30-70	30-80	2.0-3.0	80-135
1-3 yrs	40-70	20-70	30-70	1.5-2.5	80-130
4-8 yrs	35-65	20-30	30-50	1.3-2.0	50-120
9-13 yrs	30-60	20-30	25-40	1.2-1.8	40-90
14-18 yrs	15-50	10-30	15-30	1.2-1.8	35-70
19 yrs+	15-50	10-30	15-30	1.1-1.7	35-45

Table 10 Selected Medical Foods for MSUD [22, 25].

Company	Infant Products	Pediatric Products		Protein Free Modulars
		Complete	*Incomplete	
Abbott	Ketonex-1®	Ketonex-2®		Pro-Phree®
Cambrooke		Vilactin AA Plus™	Camino Pro MSUD Drink™	
Mead Johnson	BCAD 1®	BCAD 2®		PFD Toddler (Infant) ® PFD 2 (Pediatric)®
Nutricia	MSUD Anamix® Early Years	Complex Jr MSUD® Drink Mix MSUD Lophlex® LQ Complex Essential MSD Drink Mix®	Complex Essential MSD Amino Acid Blend® MSUD Maxamum®	Duocal® Polycal®
Vitaflo		MSUD Express™ MSUD Explore5™	MSUD gel™ MSUD Cooler™ MSUD Express™	S.O.S™ 10,15, 20, 25

Abbott Nutrition, Lake Forest, IL; Cambrooke, Ayer, MA; Mead Johnson Nutrition, Evansville, IN; Nutricia North America, Rockville, MD; Vitaflo USA, Alexandria, VA. *Incomplete formulas are low in or devoid of fat, carbohydrate, vitamins and/or minerals.

During illness, serious injury, or surgery, aggressive nutrition management is provided to prevent or reverse catabolism by removing or significantly reducing leucine intake, supplying adequate energy (1.5-3 times the EER), increasing BCAA-free protein (2.0-3.5 g/kg from medical food), increasing valine and isoleucine supplementation, and adding hypertonic saline with appropriate electrolytes and insulin to prevent hyperglycemia [22, 24, 26]. Avoiding hypotonic saline in IV fluids

prevents cerebral edema [22, 26]. During acute nutrition management, calorie and protein needs are typically met with continuous nasogastric feedings of MSUD medical foods (Table 10) and peripheral administration of dextrose and IV lipids [22, 26]. BCAA-free parenteral nutrition solutions are available from specialty compounding pharmacies if the patient cannot tolerate enteral nutrition; however, the patient still requires valine and isoleucine supplementation [22]. Leucine from intact protein is reintroduced or increased to baseline when elevated plasma leucine decreases to the upper limit of the treatment range: 200 µmol/L for infants and children ≤5 years of age and 300 µmol/L for individuals >5 years of age [22].

Patients with MSUD require frequent laboratory monitoring, including leucine, valine, isoleucine, prealbumin, CBC, CMP, ferritin, iron, folate, 25-OH vitamin D, trace minerals, and others as clinically indicated [22].

2.5 Phenylketonuria (PKU)

PKU was the impetus for newborn screening and inspired expanded newborn screening globally [2]. PKU is an autosomal recessive inborn error of phenylalanine metabolism, which is due to a deficiency in the tetrahydrobiopterin-dependent enzyme phenylalanine hydroxylase (PAH) in the conversion of amino acid phenylalanine (Phe) to amino acid tyrosine (Tyr) [27]. This deficiency leads to the accumulation of neurotoxic phenylalanine. Elevated phenylalanine concentrations are used to flag potential PKU patients on NBS [28]. These patients require follow-up plasma amino acid analyses as well as genetic testing to confirm the diagnosis, with an incidence of 1:10,000 in the United States [28]. European countries and the United States indicate newborns with plasma Phe concentration >360 µmol/L should start a low-Phe diet immediately [27].

Patients with classic PKU appear asymptomatic at birth; however, if a low-Phe diet is not started within the first few weeks of life, irreversible intellectual disabilities, seizures, behavioral abnormalities**,** eczema, "musty" odor, and hypopigmentation of the skin, hair, and irises develops [28, 29]. Treatment of PKU involves severe Phe restriction from food and supplementation of Phe-free medical food while optimizing growth, development, nutritional adequacy, and mental functioning by maintaining blood Phe concentrations between 120-360 µmol/L (Table 11, Table 12) [27, 30, 31]. This low-Phe diet is necessary for the patient's lifetime [27]. Patients with classic PKU receive most of their dietary protein from synthetic medical foods lacking Phe (Table 12) and a small amount of protein from vegetables, fruit.

Table 11 PKU Nutrient Needs by Age [29, 31].

Age	Phenylalanine mg/day	Tyrosine mg/day	Protein g/kg/day
0-3 months	130-430	1000-1300	2.5-3.0
3-6 months	135-400	1400-2100	2.0-3.0
6-9 months	145-370	2500-3000	2.0-2.5
9-12 months	135-330	2500-3000	2.0-2.5
1-4 years	200-320	2800-3500	1.5-2.0
4 years+	200-1100	4000-6000	120-140% DRI

Table 12 Selected Medical Foods for PKU [29, 31].

Company	Infant Products	Pediatric Products Complete	*Incomplete
Abbott	Phenex-1®	Phenex-2®	
Cambrooke		**Glytactin BetterMilk™15 **Glytactin RTD™ 10, 15, Lite **Glytactin BUILD™ 10, 20/20 **Glytactin™10 Complete Bar **Glytactin Restore™10 Powder, Lite, Lite Powder **Glytactin SWIRL™15 Phenactin AA Plus™	
Mead Johnson	Phenyl-Free 1®	Phenyl-Free 2® Phenyl-Free 2HP®	
Nutricia	Periflex Anamix Early Years®	Periflex Jr Plus® PhenylAde Essential Drink Mix® **PhenylAde GMP Drink Mix® **PhenylAde GMP Ready®	Phenylade MTE Amino Acid Blend® PKU Lophlex® LQ & Powder XPhe Maxamum® Phlexy-10® Powder, Tablets, Drink Mix **PhenylAde GMP Mix-In®
Vitaflo		PKU Gel™ PKU Trio™	PKU Express™ 15, 20 PKU Cooler™ 10, 15, 20 PKU Air® **PKU SPhere™ 15, 20

Abbott Nutrition, Lake Forest, IL; Cambrooke, Ayer, MA; Mead Johnson Nutrition, Evansville, IN; Nutricia North America, Rockville, MD; Vitaflo USA, Alexandria, VA. *Incomplete formulas are low in or devoid of fat, carbohydrate, vitamins and/or minerals. **Glycomacropeptide (GMP) product.

Recently, advances in the traditional PKU diet have increased diet compliance and provided more nutritionally complete products. In the last several years, the incorporation of naturally low-Phe and whey-based glycomacropeptide (GMP) derived from the cheese manufacturing process into metabolic foods has changed the way we think about medical food formulation (Table 12) [32]. Additionally, metabolic clinics have started implementing the Simplified PKU Diet, which promotes healthy food choices, increases flexibility, and is easier to manage than a traditional low-Phe diet [33]. The Simplified PKU Diet involves reducing the patient's specific Phe allowance from foods by about 30% and then allowing unmeasured intake of "free foods" (fruits, vegetables, foods with <75 mg Phe/100 g, and specialty low protein foods with <20 mg/serving) [29, 33].

Treatment of PKU also involves medications in addition to a low-Phe diet. Sapropterin dihydrochloride is a synthetic form of the PAH cofactor Tetrahydrobiopterin (BH_4) and enhances residual PAH activity, which allows for increased Phe tolerance (Table 13) [27]. Typically, patients with a high residual activity of the PAH enzyme have a greater probability of response to sapropterin dihydrochloride [27]. Response to sapropterin dihydrochloride is determined individually; however, response is typically defined as a ≥30% decrease of blood Phe [31]. Sapropterin dihydrochloride-responsive patients can increase their daily Phe intake, but almost all patients still require Phe restriction and Phe-free medical foods [27]. Pegvaliase (Table 13), on the other hand, is a newly FDA-approved daily injectable phenylalanine ammonia lyase enzyme substitution for PAH, and is used to treat non-pregnant adults with plasma Phe ≥600 µmol/L [30, 34]. Phenylalanine ammonia lyase converts phenylalanine into ammonia and trans-cinnamic acid to be safely excreted in the urine [30, 34]. Patients on pegvaliase can significantly increase their daily Phe intake and decrease their Phe-free medical food intake [30, 34]. While pegvaliase allows for relaxation of the low-Phe diet, pegvaliase therapy does have a high risk for side effects ranging from injection site irritation to anaphylaxis and requires thorough education and monitoring by the medical team [30, 34].

Patients with PKU require frequent laboratory monitoring, including weekly Phe and Tyr in infancy and then weekly to monthly after; plasma amino acids, prealbumin, ferritin, 25-OH vitamin D, and complete blood count (CBC) every 6-12 months; and B_{12}, MMA, red blood count, folate, iron, zinc, copper, and essential fatty acids as indicated [29, 30].

Table 13 Common Medications used to treat PKU [29, 31].

Medication	Mechanism of Action
KUVAN®[a] (sapropterin dihydrochloride)	Synthetic form of PAH cofactor BH4
JAVYGTOR™[b] (sapropterin dihydrochloride)	Synthetic form of PAH cofactor BH4
Sapropterin dihydrochloride[c]	Synthetic form of PAH cofactor BH4 (Generic)
PALYNZIQ®[a] (pegvaliase-pqpz)	Phenylalanine ammonia lyase enzyme substitution for PAH

[a]BioMarin Pharmaceutical, Novato, CA; [b]Cycle Pharma, Boston, MA; [c]PAR Pharma, Woodcliff Lake, NJ

2.6 Propionic Acidemia (PA) and Methylmalonic Acidemia (MMA)

Propionic Acidemia (PA) and Methylmalonic Acidemia (MMA) are autosomal recessive disorders resulting from a deficiency of the enzymes propionyl-CoA carboxylase (PCC) or methyl malonyl-CoA mutase (MUT), respectively, in the metabolism of propiogenic amino acids isoleucine (Ile)**,**

methionine (Met)**,** threonine (Thr)**,** valine (Val) and odd chain fatty acids [35, 36]. Deficiency in biotin-dependent PCC leads to an accumulation of propionic acid and propionyl-CoA, and a deficiency in B_{12}-dependent MUT leads to an accumulation of methylmalonyl-CoA and methylmalonic acid [35, 36]. MMA can also be caused by a defect in the transporter or synthesis of the MUT enzyme cofactor, cobalamin (Cobalamin A, Cobalamin B, or Cobalamin D-MMA), or deficiency of the enzyme methylmalonyl-CoA epimerase [36]. In Western populations, the estimated incidence of MMA ranges from 1:48,000 to 1:61,000 births and from 1:50,000 to 1:500,000 births for PA [37].

Patients suspected to have PA or MMA are flagged through newborn screening with elevated propionyl acylcarnitine and followed up with plasma homocysteine and B_{12} in addition to urine organic acid analysis [36]. PA patients will have elevated urine 3-OH Propionic acid and normal plasma homocysteine [36]. MMA patients will have elevated urine methylmalonic acid and normal plasma homocysteine [36]. Plasma homocysteine, methylmalonic acid, and serum vitamin B_{12} will be elevated in the cobalamin C, D, and F deficiencies [36].

Patients with PA or MMA present with metabolic acidosis, hyperammonemia, hyperglycinemia, vomiting, poor feeding, hypotonia, cerebral edema, and death without aggressive management. Patients are at risk for metabolic stroke, seizures, acute or chronic pancreatitis, cardiomyopathy (PA), and chronic renal impairment (MMA) that can progress to renal failure [35].

Treatment of PA and MMA includes preventing catabolism; restricting propiogenic amino acids Ile, Met, Thr, and Val while balancing intact protein and essential amino acid medical food (Table 14 and Table 15); aggressively treating illnesses; maintaining normal plasma amino acid concentrations; and supplementing with L-Carnitine, 5-20 mg daily Biotin (PA -only if responsive), and 1-2 mg daily-weekly oral or IV B_{12} (MMA-only if responsive) (Table 16) [36]. The protein goal is adjusted based on age, ammonia, and plasma amino acid concentrations. While it is necessary to restrict Ile, Met, Thr, and Val from food, it is crucial to optimize intake from intact protein sources and only use propiogenic amino acid-free medical foods when necessary [38].

Table 14 MMA/PA Nutrient Needs by Age [36, 39].

Age	Intact Protein g/kg/day	Total Protein g/kg/day	Energy Kcal/kg/day
0-3 months	0.9-1.5	1.5-1.8	72-109
3-6 months	0.9-1.5	1.5-1.8	72-109
7-17 months	0.7-1.2	1.2-1.4	64-97
1- years	0.6-1.05	1.0-1.2	66-99
4-8 years	0.57-0.95	0.95-1.1	56-88

Table 15 Selected Medical Foods for MMA/PA [36, 40].

Company	Infant Products	Pediatric Products		Protein Free Modulars
		Complete	*Incomplete	
Abbott	Propimex-1®	Propimex -2®		Pro-Phree®
Cambrooke		Promactin AA Plus™ – Berry		

Mead Johnson	OA1®	OA2®		PFD Toddler (Infant) ® PFD 2 (Pediatric)®
Nutricia	MMA/PA Anamix Early Years®	MMA/PA Anamix Next®	XMTVI Maxamum®	Duocal® Polycal®
Vitaflo			MMA/PA gel™ (1-10 y.o.) MMA/PA express™ (3 y.o – adults) MMA/PA cooler™ (3 y.o – adults)	S.O.S™ 10, 15, 20, 25

Abbott Nutrition, Lake Forest, IL; Cambrooke, Ayer, MA; Mead Johnson Nutrition, Evansville, IN; Nutricia North America, Rockville, MD; Vitaflo USA, Alexandria, VA. *Incomplete formulas are low in or devoid of fat, carbohydrate, vitamins and/or minerals.

Table 16 Common Medications/Supplements to Treat PA/MA [36, 40, 41].

Medication/Supplement	Mechanism of Action	Considerations
L-carnitine	Binds with toxic Acyl-CoA metabolites and excretes them through urine	Excessive L-carnitine is associated with a fishy odor, gastrointestinal symptoms, and may increase the risk of atherosclerosis [20]
Biotin	Cofactor for deficiency enzyme (PCC) in PA	May result in increased natural protein tolerance, but response is variable
B_{12}	Cofactor for deficiency enzyme (MUT) in MMA	Intramuscular Hydroxocobalamin Injection Typically, only Cobalamin C form of MMA is responsive and may not require dietary restriction
BuPhenyl®[a] (sodium phenylbutyrate)	Conjugates with glutamine in the liver and the kidney to increase nitrogen excretion as Phenylacetylglutamine	Typically used only during acute illness
Sodium Benzoate	Binds with glycine to form hippuric acid, which is then excreted in the urine	Typically used only during acute illness
Ammonul®[b] (sodium phenylacetate + sodium benzoate)	IV drug is only used during hospitalization. Replaces BuPhenyl and/or Sodium Benzoate	Typically used only during acute illness
CARBAGLU®[c] carglumic acid	Synthetic N-acetylglutamate synthase	In clinical trials to determine effectiveness in reducing secondary hyperammonemia in MMA and PA patients

Metronidazole	Antibiotic	Reduces bacterial propionate production – low quality of evidence for benefit

[a]Horizon Therapeutics, San Fransisco, CA; [b]Bausch Health Companies, Bridgewater, NJ; [c]Recordati Rare Diseases, Lebanon, NJ

During illness, serious injury, or surgery, calories are increased 20-50 percent above baseline needs using non-protein modulars (Table 15), dextrose-containing fluids are provided at 1.5 times maintenance fluid needs, and protein is eliminated or reduced to 50 percent for a maximum of 48 hours depending on ammonia concentration and clinical symptoms [36]. IV lipids can be added as additional calories to prevent catabolism, especially if the patient cannot tolerate enteral intake [36]. Additionally, propiogenic amino acid-free parenteral nutrition solutions are available from specialty compounding pharmacies if the patient cannot tolerate enteral nutrition or is *nil per os* (NPO). Nitrogen scavenging medications (Table 16) decrease ammonia concentrations in the hospital setting and may be required long-term, depending on chronic ammonia concentrations. After 24-48 hours, protein is slowly reintroduced and increased to well-day protein allowance to prevent refractory hyperammonemia due to protein deficiency.

Patients with PA or MMA require frequent laboratory monitoring, including plasma amino acids, ketones, carnitine, kidney function tests (MMA), prealbumin, CBC, 25-OH Vitamin D, B_{12}, folate, B_6, zinc, selenium, and ferritin as well as echocardiograms (PA) [36].

2.7 Urea Cycle Disorders (UCDs)

Urea cycle disorders (UCDs) are autosomal recessive (except for X-linked ornithine transcarbamylase deficiency) inborn errors of metabolism due to a deficiency in one of the essential enzymes required to convert toxic ammonia into benign urea [42]. Deficiency in any of these enzymes (Table 17) leads to the accumulation of ammonia, causing neurotoxicity, poor feeding, failure to thrive, vomiting, seizures, lethargy, liver dysfunction, coma, and death [42]. Patients with Arginase deficiency, however, are typically less characterized by acute hyperammonemia crises but instead experience spastic diplegias and intellectual disability. Patients with UCDs are detected through NBS by measuring elevated plasma amino acids specific to each disorder (Table 17). Carbamoyl phosphate Synthetase Deficiency and Ornithine Transcarbamylase Deficiency are not routinely on the NBS panel despite being two of the most severe urea cycle disorders and are therefore diagnosed clinically based on symptoms as well as elevated orotic acid and low citrulline concentrations [42]. The overall incidence of UCDs is approximately 1:35,000 births, which is relatively common (Table 16) [42]. Treatment includes preventing catabolism, restricting overall protein while balancing intact protein and essential amino acid medical food (Table 18 and Table 19), supplementing with citrulline (except for Citrullinemia type I and Argininosuccinate Lyase Deficiency) or arginine (except for Arginase Deficiency), and providing nitrogen scavenging medications to maintain normal ammonia concentrations for age and plasma amino acid concentrations [42]. Nitrogen scavengers help remove nitrogen and prevent hyperammonemia by utilizing alternate pathways, allowing patients to increase their protein tolerance (Table 20) [42].

Table 17 Genetics and Presentation of UCDs [43, 44].

UCD	Gene	Significant Plasma Biomarkers	Estimated Incidence
Nacetylglutamate Synthetase Deficiency (NAGS)	*NAGS*	Elevated ammonia, low citrulline, low arginine, normal orotic acid	<1:2,000,000
Carbamoyl phosphate Synthetase Deficiency (CPS)	*CPS1*	Elevated ammonia, elevated glutamine, low citrulline, normal orotic acid, low arginine	1:1,300,000
Ornithine Transcarbamylase Deficiency (OTC)	*OTC* X-linked	Elevated ammonia, elevated glutamine, elevated orotic acid, elevated ornithine, low citrulline, low arginine	1:56,500
Argininosuccinate Synthetase Deficiency (ASS) or Citrullinemia type I	*ASS1*	Elevated ammonia, elevated glutamine, elevated citrulline, low arginine	1:250,000
Argininosuccinate Lyase Deficiency (ASA/ASL)	*ASL*	Elevated ammonia, elevated glutamine elevated arginosuccinate, elevated citrulline, low arginine	1:218,750
Arginase Deficiency (ARG)	*ARG1*	Rarely elevated ammonia, elevated arginine	1:950,000

Table 18 UCD Nutrient Needs by Age [42, 44].

Age	Intact Protein g/kg/day	Essential Amino Acid (Medical food) g/kg/day	Total Protein g/kg/day
0-1 year	0.8-1.1	0.4-1.1	1.2-2.2
1-7 years	0.7-0.8	0.3-0.7	1.0-1.2
7-19 years	0.3-1.0	0.4-0.7	0.8-1.4
>19 years	0.6-0.7	0.2-0.5	0.8-1.0

Table 19 Selected Medical Foods for UCDs [44].

Company	Infant Products	Pediatric Products	Protein Free Modulars
Abbott	Cyclinex-1®	Cyclinex-2®	Pro-Phree®
Mead Johnson	WND 1®	WND 2®	PFD Toddler (Infant)® PFD 2 (Pediatric)®
Nutricia		UCD Anamix Jr® Essential Amino Acid Mix®	Duocal® Polycal®

Vitaflo	UCD trio™	S.O.S™
	EAA supplement™	10, 15, 20, 25

Abbott Nutrition, Lake Forest, IL; Mead Johnson Nutrition, Evansville, IN; Nutricia North America, Rockville, MD; Vitaflo USA, Alexandria, VA

Table 20 Common Medications used to treat UCDs [44].

Medication/Supplement	Mechanism of Action
Arginine	For use in ASS and ASA/ASL Arginine becomes conditionally essential in these disorders Arginine is supplemented to meet the body's requirement for anabolism and to enhance waste nitrogen excretion
Citrulline	For use in CPS and OTC Uses additional nitrogen to synthesize arginine from citrulline
BuPhenyl®[a] (sodium phenylbutyrate)	Conjugates with glutamine in the liver and the kidney to increase nitrogen excretion as Phenylacetylglutamine
Sodium Benzoate	Binds with glycine to form hippuric acid, which is then excreted in the urine
Ravicti®[a] (glycerol triphenylbutyrate)	Conjugates with glutamine in the liver and kidney to increase nitrogen excretion as Phenylacetylglutamine
Ammonul®[b] (sodium phenylacetate + Sodium Benzoate)	IV drug is only used during hospitalization. Replaces BuPhenyl, Ravicti, and/or Sodium Benzoate
CARBAGLU®[c] (carglumic acid)	Synthetic N-acetylglutamate synthase used for NAGS deficiency

[a]Horizon Therapeutics, San Fransisco, CA; [b]Bausch Health Companies, Bridgewater, NJ; [c]Recordati Rare Diseases, Lebanon, NJ

During illness, serious injury, or surgery, additional fluids are provided at 1.5 times maintenance fluid needs, calories are increased 20-50 percent above baseline needs using non-protein modulars (Table 19), and protein is eliminated or reduced to 50 percent for a maximum of 24 hours depending on ammonia concentration and clinical symptoms. During severe hyperammonemic crises, dialysis may be required to normalize ammonia concentrations [42].

Patients with UCDs require routine laboratory monitoring, including plasma amino acids, ammonia, 25-OH vitamin D, complete blood count, ferritin, iron, folate, selenium, and zinc [42]. Plasma amino acids and ammonia are monitored weekly in infancy and then spaced monthly as the patient stabilizes on their treatment. Maintaining plasma amino acids within goal ranges, especially glutamine, is essential given protein restriction and the potential for medications to lower branched-chain amino acids. Protein deficiency can lead to refractory hyperammonemia.

3. Conclusions

Newborn screening and medical nutrition therapy play integral roles in the treatment of inherited metabolic disorders. The expansion of newborn screening has allowed for the inclusion of a wide range of disorders, which have shown significant improvements in outcomes when detected

and treated early. Coupled with medical nutrition therapy, which provides appropriate nutrition to support growth and development while limiting the offending substrate, these interventions offer a comprehensive approach to managing inherited metabolic disorders. Continued research and advancements in newborn screening and nutrition therapy will enhance our ability to diagnose and manage inherited metabolic disorders, ultimately improving patients' long-term outcomes and quality of life.

Author Contributions

MKN and SK conceptualized the manuscript. MKN drafted the initial manuscript. MKN and SK reviewed and revised the manuscript.

Competing Interests

MKN is a speaker for Ultragenyx Pharmaceutical Inc.

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